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Disease-a-Month

Parkinsonism

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Maxwell Finland—CHEMOPROPHYLAXIS OF INFECTIOUS DISEASES (PART I)

J. Willis Hurst and *Robert Schlant*—CORONARY ATHEROSCLEROSIS AND ITS MANAGEMENT

Eugene A. Stead, Jr.—HYPERVENTILATION

Kenneth M. Moser—USE OF ANTICOAGULANT AND FIBRINOLYTIC AGENTS

S. Magnusson and *W. C. Moloney*—MULTIPLE MYELOMA

Martin M. Cummings and *Max Michael, Jr.*—SARCOIDOSIS

H. B. Mulholland, John A. Owen, Jr. and *J. Brookins Taylor*—COMPLICATIONS OF DIABETES MELLITUS

Maxwell Finland—CHEMOPROPHYLAXIS OF INFECTIOUS DISEASES (PART II)

Robert P. McCombs—PERIARTERITIS NODOSA AND RELATED DISORDERS OF BLOOD VESSELS

Maxwell Finland—CHEMOPROPHYLAXIS OF INFECTIOUS DISEASES (PART III)

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Parkinsonism

RUSSELL N. DEJONG

TABLE OF CONTENTS

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IN 1817 JAMES PARKINSON, a London physician, published a booklet of 66 pages entitled *An Essay on the Shaking Palsy*. This was mainly a clinical description of a group of patients with "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellects being uninjured." There were some hypothetical statements regarding etiology and treatment, but no anatomic or pathologic studies. In his preface, Parkinson apologized for these deficiencies but stated that he felt that delay in publication was not "warrantable" and expressed the hope "that these friends to humanity and medical science, who have already unveiled to us many of the morbid processes by which health and life is abridged, might be excited to extend their researches to this malady." Parkinson's description of this disease, which has since been given his name, was so clear and precise, and his clinical observations and delineation so specific, that this monograph has become a classic in medical literature and has twice been reprinted, the last time in 1955 on the bicentenary of Parkinson's birth (7).

Despite 150 years of study, there are still many unanswered questions about this disease. Parkinson spoke of it as "shaking palsy" and also used the Latinized term "paralysis agitans." These terms have survived through the years as the common lay and

medical names, respectively, for the condition. Charcot was the first to use the term "Parkinson's disease" (7). Gowers (28) was reluctant to accept the latter name, which, he stated, "conveys only a knowledge of a historical accident"; but he also objected to the terms "shaking palsy" and "paralysis agitans," inasmuch as they do "not recognize the rigidity, which is a more frequent feature than either the tremor or the weakness." It does seem, however, that this is one of the few situations in which we are justified in adopting the eponymic terminology, and the name "Parkinson's disease" has largely replaced "paralysis agitans" in medical usage. Critchley (7) has stated: "Parkinson's disease is an apt and indeed unassailable synonym for paralysis agitans. It is even better in many ways, for 'paralysis' is scarcely an adequate term, and the adjectival 'agitans' may be inaccurate." One of the developments through the years, however, is the growth of the concept that there may be multiple causes for what was first known as paralysis agitans and that the condition is a syndrome due to many causes and not a disease per se. Consequently, there has developed a tendency to use the term Parkinsonism for the symptom complex and to speak of the idiopathic, postencephalitic and other varieties of Parkinsonism.

INCIDENCE

Because Parkinsonism is a syndrome with insidious onset and progression, usually in the second half of life, and because in itself it is rarely fatal, the exact incidence is not known. The diagnosis is often made fairly late in the course of the disease, and undoubtedly there is a wide variation among physicians regarding criteria for the definition of the syndrome. As a result, there is much variability in estimates of its prevalence. Mjönes (22) gave the incidence in Sweden as 1.6 per 1,000 of the population of those aged 50 and over. Garland (13) found that there were 288 cases in Leeds, England, and the surrounding area, with an incidence of 1 in 1,700; he suggested an approximate total of 27,000 cases in Great Britain. Kurland (18), basing his conclusions on mortality statistics from the United States and Canada and on a detailed morbidity survey in a specific community (Rochester, Minnesota), stated that each year 1 per

4,000 of the total population and 1 in each 1,000 in the population aged 50 or over are newly affected. For the United States, this represents an incidence of about 34,000 new cases per year. He further stated that at any one time the number of clinically identifiable cases is about 1.8 per 1,000 of the population and nearly 1 per cent for those aged 50 and over. He estimated that in the United States as a whole there were 266,000 clinically identifiable cases. David DeJong (8), studying morbidity and mortality figures in Canada, reported on a Canadian Sickness Survey made in 1950–51. According to this survey, the general morbidity rate for paralysis agitans was 0.3 per 1,000 persons for all age groups, 0.85 per 1,000 in the age group 45–64 and 1.52 per 1,000 in the age group over 65. He concluded, however, that statements regarding morbidity must at the present time be only estimates; and he suggested that in the population at large there is an incidence of 0.1% and that in the older age groups an incidence of 1.0% or more is not improbable. Mortality statistics do not give sufficiently reliable information. The disease does affect individuals of all races and economic and social levels, and it is seen in all countries. On the basis of clinical observation, without statistical confirmation, the incidence is slightly higher in people of Jewish ancestry, and the disease seems to occur less frequently in the Negro than in the white race. It affects males more often than females, especially when the onset occurs before the age of 50 years.

ETIOLOGY

The etiology of Parkinsonism is complex. Paralysis agitans, as originally described by Parkinson, is a chronic and progressive disease affecting mainly those in the late middle and older age groups. It was for a long time considered to be a specific clinical entity, possibly the expression of an inherent weakness or a premature aging process localized to certain neuronic systems of the brain, the specific cause for which was not known. A history of the same disease in other members of the family is found in from 4 to 16% of cases (11). It is the opinion of most clinicians, however, that, while there is a genetic factor in some instances, this is quite uncommon. A history of trauma or of severe emo-

tional stress preceding the onset of symptoms is occasionally encountered. As with most slowly progressive diseases, it is difficult to know whether these are exciting or precipitating factors, whether unrecognized Parkinsonism was already present before the accident or other incident or whether the trauma or emotional shock may have decreased the ability of the patient to compensate for his disability. Many neurologists have had the experience of discovering the earliest evidence of Parkinsonism in a patient being examined for some unrelated condition, who at the time of examination had no symptoms referable to his signs.

With the passage of time and the continued study of this disorder, it became apparent that symptoms and signs of Parkinsonism, often difficult to differentiate from those of paralysis agitans per se, may develop in association with specific and known etiologic factors. It was observed, for instance, following the epidemic of encephalitis lethargica that occurred shortly after World War I, that persons who had suffered from this disease, and oftentimes had apparently recovered, later developed a picture quite typical of Parkinson's disease, although in most instances with the onset of symptoms much earlier in life. Occasionally there was a long latent period between the original illness and the development of Parkinsonism. It has also been observed that persons somewhat older than those normally developing paralysis agitans show signs compatible with Parkinsonism but, in addition, show evidences of diffuse and cerebral arteriosclerosis. At the present time, most clinicians and textbooks classify Parkinsonism into three major types—idiopathic, postencephalitic and arteriosclerotic. The diagnosis of and differentiation between these varieties will be discussed below, under the clinical features and symptomatology of the disorder. In addition to these three varieties, it is known that carbon monoxide, carbon disulfide, manganese and other toxins may produce a syndrome resembling Parkinson's disease; but cases having such an origin are uncommon. Brain tumors, anoxia, electric shock, syphilis and severe focal trauma have also been reported to cause Parkinsonism; but such cases are rare and may be coincidences, the patient actually having two separate, unrelated disorders. During recent years, signs and symptoms of Parkinsonism have been observed during therapy with reserpine, chlorpromazine and

barbiturates. With the increased use of these compounds, these side reactions may become an even greater problem; but, fortunately, in the majority of patients the symptoms of Parkinsonism are transient and reversible and they decrease or disappear promptly when the drug is discontinued or its dosage is decreased.

PATHOLOGY

The nature of the pathologic lesions responsible for Parkinsonism is not completely known. Parkinson himself made no postmortem study of the disease. In many of the cases that have been reported, the necropsy findings are so meager and indefinite as to leave in doubt the basic pathologic process. The paucity of histologic changes in the nervous system led Charcot, Strümpell and others to consider the disease as a neurosis, one without basic pathology; but its relentless course and the failure of all attempts to cure it by psychotherapy prevented most neurologists from accepting this theory. With the increasing understanding of the physiology of the motor system, it came to be recognized that the cause of the symptoms was most likely to be found in some part of the nervous system other than the corticospinal pathways; and attention was centered on the basal ganglia, the thalamus and the subthalamic and hypothalamic nuclei. Because of presumptive evidence of involvement of these structures in Parkinsonism and because of its resemblance in certain aspects to other hyperkinetic disorders which are also associated with pathologic alterations in these structures (the choreas, Wilson's disease, athetosis, dystonia, etc.), it and they have been classified as diseases of the so-called extrapyramidal system.

What is often referred to clinically as the extrapyramidal complex is probably not an anatomic or physiologic entity but a functional concept, the understanding of which has been derived mainly from clinicopathologic data on diseases characterized by disturbances of tone, movement and posture (10). It has been referred to as the "old motor system," and its major anatomic components are generally considered to be certain of the basal ganglia—namely, the caudate and lenticular nuclei, the latter consisting of the putamen and globus pallidus. The nomenclature of these nuclei varies: the caudate and putamen are frequently

referred to as the "striatum," and the globus pallidus as the "pallidum." Other structures functionally and clinically related to the basal ganglia are the subthalamic nucleus, the substantia nigra, the red nucleus, the inferior olivary body and the reticular formation in the midbrain, pons and medulla. There are intricate and complex anatomic connections among these structures and also between them and the motor areas in the cerebral cortex, the thalamus and the cerebellum. Discharges from these structures to lower centers are indirect and probably take place by means of relays (Fig. 1).

A detailed history of the development of our concepts of the pathologic basis for Parkinsonism will not be given, but certain of the major milestones will be recorded. Recent thorough surveys include those by Benda and Cobb (2), Heath (17) and Greenfield (15). Jelgersma (1908) was one of the first to search in the appropriate site, finding, in Parkinson's disease, atrophy of the lenticular nucleus and thalamus, as well as degenerative changes in the striothalamic fiber systems and the projections of these structures to the midbrain. In 1912 Wilson pointed out the analogies between progressive lenticular degeneration and paralysis agitans, suggesting that the cause for the latter should be found in the same general region as that for the former. Lewy, in 1912 and 1913, studied 25 cases of paralysis agitans and described cell atrophy and glial overgrowth in the caudate, putamen and globus pallidus and degeneration of the descending pathways; he likened the lesions to those found in senility. He found, in addition, spherical inclusions resembling corpora amylacea in certain brain-stem structures; these later came to be known as "hyaline bodies." Hunt, the Vogts, Bielschowsky, Alzheimer, Jakob and others described changes similar to those listed above, stressing that the morbid anatomy of the disease was in essence a chronic degeneration of cells and fibers in the striatum and pallidum and their efferent projection system (10).

Detailed pathologic studies of the cases of postencephalitic Parkinsonism showed some changes in the basal ganglia and their connections but more prominent changes in the substantia nigra. Then Trétiakoff and Hassler (15), among others, studying autopsy material from patients with postencephalitic Parkinsonism and those with paralysis agitans, noted that in both varieties

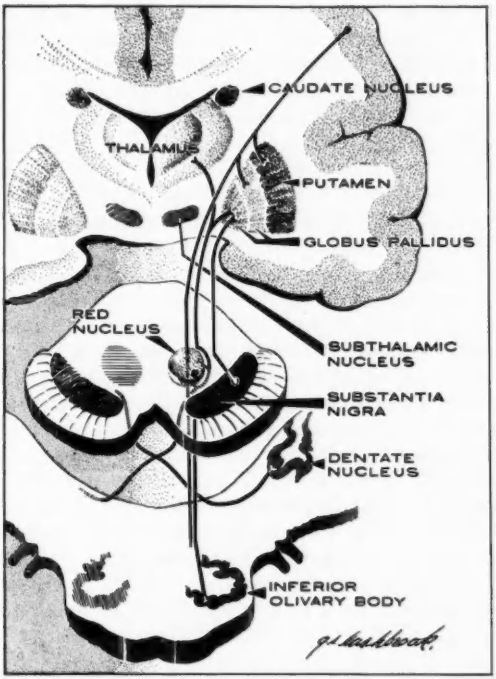

FIG 1.—Diagram of the basal ganglia and related structures, showing their major connections.

there was damage to the substantia nigra, principally a cell loss in the zona compacta. In fact, these investigators believed involvement of the substantia nigra to be more constant than that of the striatum and pallidum in both varieties. They also noted the presence of Lewy's hyaline inclusions in the substantia nigra; and Hassler, in addition, found them in locus caeruleus. Greenfield and Bosanquet (16), in one of the most recent and thorough studies, stressed the pathologic changes in the substantia nigra in both varieties. They stated that the presence of inclusion bodies in both substantia nigra and locus caeruleus was more character-

istic of idiopathic Parkinsonism, whereas neurofibrillary alterations in the pigmented cells of the substantia nigra were the essential findings in the postencephalitic variety. The most common abnormality in arteriosclerotic Parkinsonism is the presence of multiple lacunar lesions, or foci of softening and degeneration, in the striatum and pallidum, along with glial proliferation and perivascular hemorrhages; similar disease in the substantia nigra may be present but is not constant.

Although there is still lack of general agreement regarding the specific pathologic alterations in the various types of Parkinsonism, with possibly a certain degree of variability from case to case, most authorities attribute the predominant features of the symptom complex to changes, either degenerative or postinflammatory, in the basal ganglia and their connections, in the substantia nigra and in associated brain-stem structures such as the reticular formation. The histologic character of the degenerative changes in the nerve cells and the reaction to these most nearly approximate the features seen in senility, but they occur in the presenile period and are present mainly in areas other than the cerebral cortex. It is probable that multiple lesions are the rule in most instances. The individual pathologic alterations are often minimal, but widespread; and the site of predominant damage may determine whether tremor, rigidity or loss of associated movements will be most marked. Greenfield, in his last survey of the subject (15), stated that the essential feature of Parkinsonism is a systemic degeneration of a special type affecting a diffuse neuronal system, both afferent and efferent, whose nodal point is the substantia nigra, and concluded: "The cause of this neuronal degeneration remains a problem whose solution may possibly be found in enzyme chemistry, or some other new field of investigation."

PATHOLOGIC PHYSIOLOGY

The pathologic physiology responsible for the motor abnormalities of Parkinson's disease has not, as yet, been entirely explained. The earlier theories were based principally on clinical and pathologic studies, and concepts which varied widely were presented. Symptoms of extrapyramidal dysfunction are more

likely to occur with mild, diffuse damage to the basal ganglia and related structures than with large circumscribed lesions of any one portion. Neoplasms affecting these areas, for instance, rarely cause the characteristic motor manifestations. It may be that the symptoms result from partial, rather than from complete, destruction of certain structures and may be produced by slowly degenerating lesions which are capable of inducing abnormal discharges. Both involuntary movements and disturbances in tone may represent release of relatively healthy undamaged efferent neural pathways from controlling, or inhibiting, influences of other structures (10) or abnormal timing of descending extrapyramidal impulses (19).

There have been many attempts to reproduce the manifestations of Parkinsonism in experimental animals, using both destructive lesions and stimulation of the basal ganglia, thalamus and midbrain and brain-stem structures, singly and in combination; but it is questionable whether a complete replica of the syndrome has ever been produced. The closest experimental resemblance to Parkinsonism has followed the introduction of small electrolytic lesions in the lateral part of the reticular formation of the mesencephalic tegmentum between the red nucleus and substantia nigra (5, 24, 29). Part of the difficulty in obtaining true experimental Parkinsonism may be assumed when one considers the extremely complex connections of the basal ganglia and related structures, and it may be that experimental lesions of selective areas may not interrupt function in the same way as do the diffuse and scattered degenerations that have been reported clinically. These studies have, however, added to our knowledge of the functions of these structures.

It has been assumed that disturbances in tone, as well as hyperkinesias and other abnormalities of movement, may result from many different alterations of either structure or function. Rigidity may be considered to result from an abnormal bombardment of the myoneural outflow or overactivity of the gamma motor neurones. It may be caused by pallidal lesions which interrupt the normal inhibitory effect of this structure on lower reflex arcs, by impairment of conduction of impulses from the cortex to the pallidum and other basal ganglia, by combined extrapyramidal and pyramidal involvement at capsular levels, by interruption of

pallidofugal fibers, by release of lower centers from vestibular control, by impairment of function of suppressor areas or by stimulation of facilitatory centers. Hyperkinesias of various types may be caused by imbalance of the reciprocal innervation between cortical and extrapyramidal centers; by interruption at any site of the complex circuitous pathway between the cortex, basal ganglia, lower extrapyramidal centers, cerebellum, thalamus and cortex; by disease of any of the structures entering into this circuit; or by rhythmic activity of the reticular formation when it is released from the control of the higher centers by means of lesions below the basal ganglia which destroy part of the mesencephalic and pontine tegmentum. Hypokinesia, bradykinesia and loss of associated movements may be the result of rigidity alone, dependent on the extent or severity of pathologic change; it may be, however, that widespread extrapyramidal involvement interferes with the initiation or the conduction of impulses for simple automatic activities and movements of association and expression (10).

CLINICAL FEATURES

The major features of Parkinsonism are those of motor dysfunction. The cardinal symptoms consist of tremor, rigidity, and reduction or loss of spontaneous and associated movements. Most of the other manifestations of the disorder are secondary to, or variations of, these three components.

Tremor

The tremor of Parkinsonism consists of relatively rhythmic alternating contractions of opposing groups of muscles. It is insidious in onset and is sometimes palpable before being visible. It usually affects the distal muscles first, especially those of the fingers and hands. When present in these structures, it is often seen to be compound in type, consisting of alternating contractions of the flexors and extensors and of the abductors and adductors of the fingers and thumb, together with motion of the wrist and forearm, including flexion, extension, pronation and supination. As a result, there is a repetitive movement of the thumb on the first two fingers, together with motion at the wrist,

which produces the so-called "pill-rolling" or "bread-crumbling" tremor. This movement may vary in amplitude and rate; but it is usually relatively coarse and, although occasionally irregular, the rate is most characteristically from 2 to 6 per second, usually from 4 to 5 per second. The feet, jaw, tongue, lips, larynx and head may also be affected.

The tremor is usually defined as "resting," static or nonintentional; that is, it is present only or mainly while the parts are relaxed, and it disappears temporarily while the limb is engaged in some voluntary effort. While the patient is seated quietly with his arms resting on his lap or on a table, the tremor may be quite apparent in the hands; at the same time, if it involves also the feet, a tapping on the floor can sometimes be heard. When he is asked to carry out a voluntary movement, the tremor is temporarily relieved, but it appears again as soon as the movement is finished. One should bear in mind that the outstretched arms are not at complete rest but under a certain amount of muscle tension, so the tremor may or may not be present in such a position. The tremor of Parkinsonism, however, is not always a resting tremor, for sometimes it appears only, or is more marked, while the extremity is in use; that is, in some cases it is an action tremor, and on other occasions it is both a resting and an action tremor.

As is true with most of the other hyperkinesias, the tremor is absent during sleep. Although primarily a resting phenomenon, it may increase during nervous tension and when the patient is apprehensive, excited, self-conscious or feels that he is being observed. On occasion, it can be somewhat restrained by the effort of the will for a brief period of time but then increases in intensity when it reappears. It usually is not constantly present; it may diminish or disappear for a short time or may wax and wane in intensity during a period of observation.

Rigidity

Rigidity is a type of hypertonicity in which there is a state of fairly steady muscular tension equal in degree in the opposing muscle groups. It is tested for by carrying out passive motion at the joints. If present, there is resistance to such passive movement

which, in contrast to the resistance found in spasticity, is present throughout the entire range of movement and is continuous from the beginning to the end of the movement. Furthermore, it is present and constant whether the extremity is moved slowly or rapidly. This type of hypertonicity has sometimes been defined as "waxy, or lead pipe, resistance." It may vary in degree from mild to severe. It appears first in the proximal muscles, those of the neck, trunk, and shoulder and hip girdles, and later spreads to the distal ones (28). All muscles may become affected, but there is predominant involvement of those of the neck and trunk and the flexors of the extremities.

At times when the rigid extremity is being moved passively, the examiner feels a jerky intermittent resistance and the muscles seem to give way in a series of steps, as if the manipulator were moving a limb attached to a heavy cogwheel or pulling it over a ratchet. This phenomenon has been given the term "cogwheel rigidity." It probably is not a specific type of increase in tone but is due to perception of the tremor as the extremity is being moved, a combination of rigidity and superimposed tremor.

Reduction of Spontaneous and Associated Movements

Reduction of spontaneous and associated movements is the third common component of the Parkinsonian syndrome. Such reduction may be in part or entirely secondary to the rigidity (28), but some patients with only minimal rigidity will show unusual reduction in spontaneous activity. The decrease in voluntary motor activity is often referred to as "poverty of movement," or bradykinesia; if maximal, it may be termed "akinesia." There is slowing, stiffness and decrease in amplitude of all movements. The patient has difficulty in initiating activity and may get out of a chair or begin other voluntary movements slowly and after a delay. His gait, speech, writing and all other activities become slowed. The time required for the normal functions of dressing, eating and the like is greatly increased, if they are possible at all. Often it is necessary to prod the patient in order to get him to eat, exercise, care for himself or take part in family affairs. There is difficulty in performing more than one action at

one time. For example, the patient, while sitting and reading, will be unable to lay the book aside and greet a caller in a smooth, progressive fashion. The several steps in the process—that is, closing of the book, placing it on the table, rising from the chair and extending the hand—are all performed as separate acts. The patient with advanced disease may sit motionless in a chair, with his hands at rest on his lap.

Along with this loss of spontaneous movement, there is impairment of associated automatic or auxiliary movements. One of the first manifestations to appear, for instance, may be a loss of the normal swinging of the arms when walking, possibly due in part to rigidity of the shoulder girdle muscles. The patients rarely cross their legs when seated. In rising from a chair, they move slowly as in one piece, and they do not use their arms to assist them. If a standing patient is suddenly pushed backward or forward, he cannot contract the muscles necessary for the maintenance of equilibrium and he will fall in the direction he has been pushed. If the seated patient is pushed backward, he does not extend his legs and no attempt is made to counteract the loss of balance.

The loss of automatic and associated movements, as well as rigidity, is also apparent in the muscles supplied by the cranial nerves. There is a decrease in facial movements, both volitional and emotional, causing the so-called "masking" of the face. The face is smoother than normal, the features are flattened, and the expression is "set" or "wooden" (Fig. 2). Blinking of the eyelids is infrequent or absent, resulting in a staring gaze. Emotional responses are decreased in amplitude, slow in developing, but unduly prolonged when they do occur. There is, for instance, infrequent smiling and laughing; but when the patient does smile, he does so with a prolonged, "frozen" smile. Decreased frequency of normal automatic periodic swallowing contributes to the drooling of saliva from the mouth, especially when the patient is sleeping or in the erect position with the head drooping.

There is rarely any actual loss of muscle power or true paralysis in Parkinsonism, but the rigidity and decrease in speed and amplitude of movement may suggest the presence of weakness. In some cases, however, the actual strength of muscular contraction is impaired, especially in the smaller muscles. There is no

FIG. 2.—A patient with Parkinsons' disease, showing characteristic posture and facies. (From DeJong, R. N.: *The Neurologic Examination, Incorporating the Fundamentals of Neuroanatomy and Neurophysiology* [2d ed.; New York: Paul B. Hoeber, Inc., 1958], Fig. 127.)

atrophy. Even though strength may seem to be quite good on testing, there is loss of agility and dexterity of movement, as well as fatigue of muscular activity. Small movements, such as writing, buttoning, shaving, dressing and the cutting of food, are impaired; and the patient cannot rapidly carry out repeated actions, such as flexing and extending the thumb and fingers. Rigidity and decreased motor activity may lead to contractures, especially affecting the neck muscles, shoulders, elbows, wrists and fingers. The latter may be flexed at the metacarpophalangeal joints and extended at the interphalangeal joints; the ulnar deviation and "spiked" knuckles may suggest the presence of arthritis.

OTHER MOTOR MANIFESTATIONS

The other conspicuous and characteristic changes of Parkinsonism are probably combinations of the tremor, rigidity and akinesia. Some of these are as follows:

POSTURE AND GAIT.—The patient's attitude, posture and gait are quite characteristic. In the standing position, the head and trunk are bent forward with flexion at the cervical and lumbar regions, resulting in a stooped posture (Fig. 2). The arms are adducted and pronated, with flexion of the elbows, wrists and fingers. The legs are adducted, with moderate flexion of the knees. The gait is slow, rigid and shuffling, and the patient walks on his toes with small, stiff, mincing steps. The loss of arm swing interferes with stability of gait, and the adduction of the thighs narrows the base and contributes to poor balance. The stooped position and overhanging of the head causes a forward shifting of the center of gravity. Consequently, there is a tendency to fall forward when walking (propulsion or anteropulsion). The patient may take rapid steps in an attempt to keep the lower part of the body in line with the center of gravity. He also has a tendency to increase the speed when walking (festination); and he may have difficulty in stopping, once he has started walking. He may take small steps without moving, as in marking time, before he can start to walk, and then accelerate so rapidly that he cannot stop without bumping into objects or walls. The patient also has difficulty in turning or in executing an about-face, which he does by taking many small steps. He may have marked difficulty getting out of a chair without falling back into it. Sometimes this inability to get out of a chair or to initiate walking is markedly relieved by minimal assistance, such as merely touching the patient's hand. Occasionally, under adequate emotional stimulation, the rigidity and akinesia leave temporarily, and for a brief period of time the patient can perform acts for which he was otherwise incapacitated.

WRITING.—The handwriting is often markedly affected. In the first place, it is shaky and tremulous; in the second place, very small (micrographia). It is quite characteristic that the writing becomes smaller as the patient continues to write; that is, the letters in the beginning of a word or sentence may not be much smaller than would normally be expected, but as the patient writes they become smaller and smaller, gradually becoming illegible.

SPEECH.—Articulation is much disturbed; and, as it becomes less distinct, its cadence is lost and often drops to a monotone.

Syllables are slurred, and the ends of sentences fade into a mutter. Speech is usually feeble and slow, owing to muscular rigidity and immobility of the lips and tongue; it lacks modulation, and words are "chopped off." At times there is a tendency to hurry toward the ends of long words and sentences, giving the speech a festinant style. Occasionally in Parkinsonism the speech is reduced to an almost unintelligible whisper, which in some cases is the major complaint. Palilalia (involuntary repetition of words or phrases) occurs at times, but it is unusual in idiopathic Parkinsonism; in postencephalitic Parkinsonism, however, there may be both palilalia and compulsive speech, which may be affected by respiratory tics and anomalies.

OTHER MOTOR PHENOMENA.—Eye movements may be somewhat limited and interrupted by slight jerks (cogwheel phenomenon). There may also be decreased convergence and impaired upward gaze. Ocular anomalies, however, are more prominent in the postencephalitic cases. Orbicular spasms or blepharospasm may occasionally replace infrequent blinking.

At times, patients in whom immobility is prominent complain paradoxically that they "cannot sit still" and they have a tendency to move about restlessly and impatiently, frequently changing the position of the legs and hips. This has been termed "akathisia."

SENSORY SYSTEM

Parkinsonism is essentially a disturbance of the motor system, and there are no characteristic sensory changes, all modalities being preserved. Sometimes the patients do complain of aches and pains and feelings of stiffness, drawing, dragging and tightening, which can be ascribed in part at least to muscular rigidity. There are, however, no objective changes in sensation which may be considered part of the Parkinsonism itself.

REFLEXES

As a general rule, reflex action is not altered to any major degree in Parkinsonism. The deep reflexes are usually normal,

although occasionally slightly increased or decreased, the response depending to a certain extent on muscular tonicity and the amount of rigidity that is present. Early in the disease the reflexes may be slightly exaggerated, owing to increased tension of the muscles, but this is not a consistent finding; and the increasing rigidity may cause their retardation, diminution or even absence. The superficial reflexes, especially the abdominal reflexes, are occasionally moderately exaggerated, although this is not characteristic. There is often, however, very distinct exaggeration of the orbicularis oculi (glabellar) and orbicularis oris (snout) reflexes. The presence of definite reflex abnormalities, such as exaggeration of the deep reflexes and the presence of a Babinski sign or allied responses, indicates associated pyramidal tract involvement and usually is not part of Parkinsonism per se.

Autonomic Nervous System Changes

Sialorrhea is a common symptom. There is probably an increase in the production of saliva in most patients; but also, owing to the loss of associated movements and infrequent swallowing, they may drool the saliva normally present. Occasionally there is hyperhidrosis, seborrhea, dermatographia and pupillary abnormalities. All of these are more frequently seen in the postencephalitic variety.

Mental Symptoms

Intellectual functions are not characteristically impaired in Parkinson's disease. The patient may, however, be greatly fatigued by the incessant tremor throughout the waking hours, so that he reaches a state of exhaustion with impaired initiative. Also, he may be quite self-conscious and disturbed over the tremor and difficulty with movement. Consequently, symptoms of depression and irritability are not uncommon and may be considered a reaction to chronic illness or the natural outcome of an incurable ailment. Throughout the course of the disease, however, psychologic factors certainly play a prominent part in decreasing the ability of the patient to combat disability and fatigue. Probably in most advanced cases there is increasing difficulty with memory and concentration, but there is a marked

individual variation in this. Because of the slow and difficult speech, the lack of emotional display of the face and the decrease in activity and interests, the relatives and even physicians may assume that the patient's intellect is failing; this may be true in some cases and not in others. Psychotic symptoms and behavioral abnormalities are occasionally a part of the picture of postencephalitic Parkinsonism. Loss of memory and progressive intellectual deterioration are sometimes seen in the terminal states of Parkinson's disease, but these are more likely to be a part of the postencephalitic or arteriosclerotic variety and thus associated with diffuse or progressive cerebral disease other than that causing the Parkinsonism itself.

Postencephalitic Parkinsonism

The term "postencephalitic Parkinsonism" is used to describe those cases in which the symptoms develop coincidentally with, or following, an attack of encephalitis of the von Economo type; on occasion there is a long symptom-free period between the encephalitis and the onset of the Parkinsonism. There is a difference of opinion on the part of authorities regarding the separation between Parkinson's disease and the postencephalitic syndrome. Some feel that many or all cases of paralysis agitans may follow an unrecognized encephalitis, whereas others express the belief that so-called postencephalitic cases are merely instances of Parkinson's disease of early onset. Most agree, however, that they are separate diseases and that they should be distinguished because of differences in prognosis and response to treatment. While most cases have been reported to follow encephalitis of the epidemic type, the syndrome has occasionally been associated with sporadic cases of encephalitis.

In general, the clinical manifestations of postencephalitic Parkinsonism are very similar to those of paralysis agitans insofar as tremor, rigidity and loss of spontaneous and associated movements are concerned, although there are some differences. The onset of the postencephalitic type is often more abrupt, following which the symptoms may progress rapidly for a period of time and then remain more or less stationary. The tremor may be less marked than the rigidity and may be less typical and rhythmic; it is

frequently present with active movement, and it may be irregular and jerky, sometimes even with choreic or athetoid manifestations or other complex features. Other points of difference that are generally accepted are discussed in the following paragraphs.

In the first place, a history of previous encephalitis is a desirable finding in making a diagnosis of postencephalitic Parkinsonism, although sometimes such a history cannot be obtained even though the clinical picture seems to be quite characteristic. In some instances, patients have developed the Parkinsonian syndrome immediately after, or insidiously a short time after, the encephalitic illness; oftentimes, there is a latent period of not only months but even years before the development of the Parkinsonian picture. The physician should always interrogate the patient regarding possible encephalitis, especially that of the epidemic or lethargic type which occurred after World War I, with hypersomnia, fever, ocular palsies and hyperkinetic manifestations. Even though a history of such an illness may not be available, the patient may recall having had a serious illness with a prolonged period of high fever, delirium and/or coma, and mental confusion. Sometimes, instead of a period of prolonged lethargy, there may be a history of an episode during which the patient had either insomnia or inversion of the sleep cycle. Because of the temporal association of the world-wide epidemic of influenza with the subsequent widespread encephalitis lethargica during the years 1918–1923, many physicians have associated the two, believing that the latter was caused by the same virus as the former, and so they consider a history of influenza as sufficient. However, it must be stated that the virus of so-called lethargic encephalitis has never been identified; and, furthermore, its relationship to influenza has never been established. There have been a few clinical reports of the development of Parkinsonian syndromes following other specific types of encephalitis: the St. Louis variety, the western equine variety, measles encephalitis and the encephalitis associated with other diseases, such as Rocky Mountain spotted fever.

One of the important differential points between postencephalitic Parkinsonism and paralysis agitans is the earlier onset of the former, which may appear at any age from childhood on, and most frequently before age 40, whereas paralysis agitans

has its onset chiefly between the ages of 50 and 60. While the development of the clinical picture in the postencephalitic variety may be steady and progressive, as is the case with paralysis agitans, it sometimes develops more quickly and remains more or less stationary. Another extremely characteristic feature is mentioned below, under Treatment. Not only do patients with postencephalitic Parkinsonism respond more effectively to the drugs used in therapy, but they are able to tolerate a much larger amount of these drugs without side effects.

From a clinical point of view, two important characteristics which are more or less limited to postencephalitic Parkinsonism are the ocular manifestations and the hypothalamic and autonomic nervous system changes. These are doubtless associated with the predominant mesencephalic and hypothalamic site of pathologic change, which has long been recognized.

Jerkiness of ocular movements and impaired convergence have been mentioned as occurring in Parkinson's disease; the so-called cogwheel phenomenon is often more marked in postencephalitic Parkinsonism. In addition, the weakness of convergence is more profound and may lead to actual paralysis of convergence; this, on occasion, may result in diplopia. Paralysis of upward gaze may also be present. The pupils may be small and irregular, and there may be loss of the reflex response to light, suggestive of the Argyll Robertson pupil.

Two important ocular manifestations of postencephalitic Parkinsonism are oculogyric crises and attacks of blepharospasm. Oculogyric crises are attacks of involuntary conjugate upward deviation of the eyeballs (Fig. 3), occasionally with some deviation to one side; rarely the eyes may be turned downward. The attacks may be transitory or may last for hours, until the patient is able to get to sleep. He may be able to turn the eyeballs downward for short periods of time but be unable to keep them down. The deviation of the eyes may be so marked that the cornea is hidden under the lid and the sclera is all that can be seen. Some patients state that the crises come on in association with the forced or compulsive thinking of a certain apparently irrelevant but repeated word, phrase or sentence. Less common than oculogyric crises are periods of blepharospasm in which the eyes go nearly or completely shut, in some cases lasting for

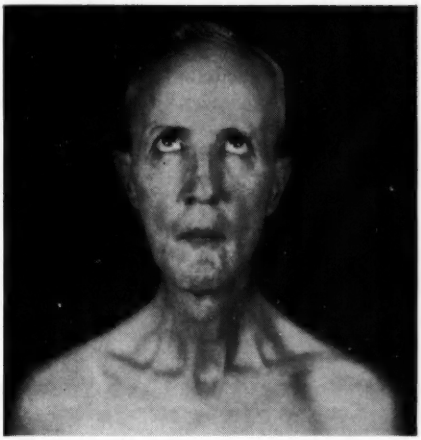

FIG. 3.—Oculogyric crisis in a patient with postencephalitic Parkinsonism. (From DeJong, R. N.: *The Neurologic Examination, Incorporating the Fundamentals of Neuroanatomy and Neurophysiology* [2d ed.; New York: Paul B. Hoeber, Inc., 1958], Fig. 62.)

long periods of time and causing the patient to be virtually blind during this interval.

Autonomic nervous system changes are often prominent. Sialorrahea is more common and more severe than in paralysis agitans. The skin of the face and forehead is often greasy and seborrheic, and there may be extensive seborrhea of the eyelids and scalp. Hyperhidrosis is commonly seen. Other hypothalamic symptoms include increase in appetite and thirst, and changes in the sleep cycle and in water, fat and glucose metabolism. Diabetes mellitus, diabetes insipidus or obesity may be seen, as may either hypersomnia or narcoleptic manifestations.

Behavioral changes may also be present. These include conduct disorders, personality abnormalities and even psychotic manifestations. Occasionally there are other, more rare, residuals of encephalitis, such as tics, spasms and respiratory disorders. Convulsions are usually evidences of cortical involvement and are rare in postencephalitic Parkinsonism.

Arteriosclerotic Parkinsonism

There is some controversy regarding whether arteriosclerotic Parkinsonism should be differentiated from the idiopathic variety. There are some clinical differences, however, and there is fairly general agreement regarding distinct pathologic alterations in the so-called arteriosclerotic type.

The onset of symptoms in arteriosclerotic Parkinsonism is later than that in paralysis agitans, usually after age 60 or in "old age." The course is a progressive one, but sometimes there are advances by exacerbation. The picture is mainly that of muscular rigidity with associated weakness and slowing of movement, loss of associated movements and progressive disturbances of gait. Tremor, if present, is less marked. The involvement most frequently affects the trunk and lower extremities to a greater degree, and the patient walks with short mincing steps but with less festination and propulsion. The gait is frequently described as the "marche á petits pas." There may be associated pseudobulbar symptoms with forced laughter and crying, pyramidal signs and evidences of focal cerebral involvement, such as aphasia, apraxia, alexia or localized paralysis. If the arteriosclerosis also affects the cerebral cortex, there may be memory loss, disorientation and confusion; and occasionally symptoms of senile dementia accompany those of motor involvement. The course may be hastened by the occurrence of minimal but repeated episodes of cerebral thrombosis or vascular insufficiency. There is usually evidence of associated arteriosclerosis, as shown in the retinal and other vessels, and often an antecedent history of hypertension, headache, cardiovascular disease or renal involvement.

Syphilitic Parkinsonism

Syphilitic Parkinsonism has been described as a specific type secondary to cerebral or cerebrovascular syphilis. There may be selective involvement of the basal ganglia and midbrain in either parenchymatous or vascular syphilis, but the positive diagnosis is difficult to make. Even pathologic studies may not entirely clarify the case and distinguish between the Parkinsonian syndrome due to syphilis or coincidental cerebral syphilis and Parkinson's

disease. True Parkinsonism attributable to syphilitic disease alone is an unproved entity.

Miscellaneous Varieties of Parkinsonism

Parkinsonism following carbon monoxide poisoning and anoxia from nitrous oxide anesthesia have been reported. In most of these cases, there was prolonged coma at the time of the intoxication or anoxia, with the immobility and apathy passing gradually into what appears to be a Parkinsonian rigidity with fixed postures and sometimes with tremors. In addition, there often is associated mental dullness, with memory loss, confusion, disorientation, convulsions and intellectual deterioration. Some of these cases have been shown at autopsy to have necrotic and other changes in the striatum and pallidum.

Workers with manganese powder, unless protected from inhalation, develop a severe Parkinsonian rigidity, with slowing of speech, after some months of exposure. The rigidity affects the trunk as well as the limbs and facies. Rhythmical tremors of the head and proximal parts of the limbs are common, although there are no characteristic pill-rolling movements. Speech and personality changes may be apparent. In some cases the symptoms more closely resemble those of pseudobulbar or bulbar paralysis than Parkinsonism. Carbon disulfide and cyanide have both been shown experimentally to produce necrosis of the pallidum, and it has been suggested that they may be responsible for Parkinsonism also. As has been mentioned above, symptoms of Parkinsonism have on occasion been reported in association with brain tumors, and also as sequelae of either focal or generalized cerebral trauma; the relationship, however, is not well understood, and, while tremor and/or rigidity may be important symptoms in these cases, it is doubtful whether such cases should be considered true instances of Parkinsonism.

CLINICAL COURSE

The manifestations of Parkinson's disease vary from case to case. In some instances, the tremor is the outstanding symptom; in others, the rigidity, the akinesia or the loss of associated movements. The onset is very often insidious, so that the time of the

earliest appearance of the symptoms may be difficult for either the patient or his associates to recall. On occasion, however, there does seem to be a rather precipitous onset of manifestations following trauma, emotional shock, surgical operations, etc. Not infrequently, the signs of the disease appear unilaterally in the beginning, with tremor, rigidity or slowing of movement affecting first one upper extremity, then going to the opposite upper extremity, then the jaw, the head, and the lower extremities. In some cases the difficulty is limited to one side of the body for a fairly long period of time before it becomes bilateral, and there are occasional cases which remain unilateral.

The course of the disease, whether it be paralysis agitans or postencephalitic or symptomatic Parkinsonism, is usually progressive, with the tremor, rigidity and akinesia becoming more severe with the passage of time. There is, however, a great deal of variability from case to case. In true Parkinson's disease, the course is most frequently a steady and progressive one; postencephalitic Parkinsonism often has its onset rather abruptly, with a rapid progression of symptoms for a period of time, after which the signs of the disease remain more or less stationary; arteriosclerotic Parkinsonism often advances by exacerbations or with a steplike increase in severity. Some patients with any of the varieties may have a rapid downhill course lasting only 2 or 3 years. Most patients become disabled sooner or later, but many are able to make an adjustment and carry on with fairly normal activities for 10 or even 15 years or longer. As the disease does progress, however, the patient becomes more and more disabled. Eventually he has increasing difficulty getting out of a chair, walking, feeding himself and taking care of his normal daily activities, and he may finally become either chairfast or bedfast. Late in the disease the patient may develop dyspnea due to reduced vital capacity, decreased respiratory strength and rigidity of the chest wall. Parkinson's disease in itself usually does not cause death; when death does occur, it is usually the result of intercurrent infections, cardiovascular complications, etc. As mentioned above, confusion, disorientation and intellectual deterioration are usually not a part of the symptom complex but may develop as preterminal or terminal manifestations, more often in the postencephalitic and arteriosclerotic varieties of the

disease. The rapidity or lack of rapidity of progression during the first months or year or two of the disease may be a valuable clue to the continued rate of progression of symptoms. Those patients in whom there is only minor worsening of symptoms during the first year or two may continue to have very slow progression; they may be able to continue with their work and usual activities for many years, and they may never be completely incapacitated. On the other hand, those in whom there is rapid progression after the symptoms first become manifest may soon become limited in their activities, have to give up their usual occupations and interests and, before long, become hopeless invalids. There is some clinical opinion, although never scientifically proved, that the drugs to be mentioned below may retard the progress of the disease as well as cause some symptomatic relief. Consequently, most physicians feel that patients should continue with their drug therapy even though the various pharmaceutical products do not give them as much relief from symptoms as might be desired.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

. The picture of Parkinsonism is so specific that the diagnosis in most cases can be made without difficulty; there are very few other conditions with which the disease may be confused. Early diagnosis, however, is somewhat difficult at times; and the physician must often use acumen to note the first minimal signs of tremor, rigidity or slowing of movement. Laboratory criteria offer no assistance, inasmuch as there are no specific blood, spinal fluid, x-ray or electroencephalographic changes.

The late Dr. Wartenberg, among others, described a few technics of testing (30) which are said to bring about early recognition of the disease. These are mainly methods of eliciting rigidity. One of these is the *head-dropping test.* With the patient lying supine without a pillow, the examiner places his left hand under the patient's occiput and with the right hand briskly raises the head and then allows it to drop. Normally the head drops rapidly into the examiner's left hand, but in patients with Parkinson's disease there is delayed, slow, gentle dropping of the head. In the test for *pendulousness of the legs,* the patient sits on the edge of a table with his legs hanging freely. The examiner either extends both legs to the same horizontal level and then releases

them or gives them a brisk push backward. In Parkinsonian rigidity there is a decrease in swinging time. In the *shoulder-shaking test,* the examiner places his hands on the patient's shoulders and shakes them briskly in both a backward and forward and a rotatory direction. With Parkinson's disease there will be a decreased range of arm swinging on the affected side. These responses are said to be characteristic, and Wartenberg has stated that they are decisive in the differential diagnosis of Parkinsonism. They are present, however, only when rigidity has reached a certain degree, and many times the diagnosis can be made by the astute examiner well before these tests become positive.

It is often difficult to describe tremor quantitatively, and even much more difficult to assess and define rigidity and akinesia objectively and quantitatively. As a consequence, many investigators have attempted to devise technics and instruments for such objective evaluation, often less as diagnostic tools than as means for evaluating response to drug, surgical and other therapy. The rate and rhythm of the tremor have been measured in various ways, using myographic and kymographic records as well as, more recently, the electromyogram. Motion-picture records are also very helpful. These do not, however, give much information about rigidity, speed and dexterity of movement or about delay in initiation of movement.

Many rather complex procedures have been described in recent years. With the use of tambours, small accelerometers, magnets, strain gauges and photoelectric cells, tremors have been recorded at rest and in fixed positions. McKinley and Berkwitz (20), using constant acceleration, developed a technic for the detection of a quantitative difference in muscle tone in patients with Parkinsonism. Spiegel and associates (26) and Agate, Doshay and Curtis (1) have devised machines that automatically record torque as a function of angular displacement of the forearm at slow constant velocities. Recently, Webster (31), using an apparatus to record rotational torque versus arm position as the forearm is alternately flexed and extended to a 100-degree arc, developed technics for dynamic measurement of rigidity, strength and tremor in Parkinsonism. Boshes and associates (3) have devised procedures for measurement of tone by a strain-gauge tonometer in dyne-centimeters of torque as the upper limb is

moved through a constant arc under controlled conditions. They record tremor by use of a variable reluctance accelerometer, an input coupler and an ink writer. These technics are all extremely complex, however, and require a great deal of apparatus. Appraisal is made more difficult by the fact that neither tremor nor rigidity is constant at all times in any one patient.

It is apparent that, for clinical evaluation, functions most closely related to the patient's disabilities should be measured. The procedures should be simple, although numerical results are desirable. Burns and David DeJong (4) have recently described a technic for testing rigidity by noting the speed of flexion and extension of the forefinger, wrist, elbow and knee: they evaluate tremor by means of the electromyogram and use simple mechanical tests for dexterity, noting the speed of simple actions, such as the placing of pins in holes. Schwab and associates (25), as a result of long experience with a large number of patients with Parkinson's disease, have assembled a battery of tests which do give important clinical information. In addition to the routine neurologic appraisal, which includes testing the speed as well as noting the characteristics of the gait, they note the length of time it takes the patient to get out of a chair and the length of time it takes to button and unbutton a piece of cloth. They test the patient's handwriting and circle-drawing and the speed of proximation of the finger and thumb in a set period of time. They make dynamometer readings, electromyograms and an electrical-tremor recording. By the use of a bulb ergograph, they evaluate speed and fatigue of voluntary movements. The foregoing tests are valuable; but equally valuable oftentimes is a questionnaire from the patient giving information about the speed of performance and the need for help in routine daily procedures, such as dressing and undressing, putting on or taking off overcoats, handling buttons, zippers and shoe laces, bathing, washing, combing the hair, brushing the teeth, shaving, the use of utensils in eating, time of eating, spilling of food, handling of doors, walking, avoiding of obstacles, getting in and out of automobiles and the ability to perform routine chores in and about the house or to keep up with hobbies and recreation.

In the differential diagnosis of Parkinson's disease and symptomatic Parkinsonism, various other conditions must be borne in

mind. Perhaps the disease is confused most frequently with familial and senile tremors. The latter, however, are usually postural or tensional tremors, worse with the hands outstretched or with activity, and are definitely increased by motor tension and fatigue. There is no rigidity, and there are no postural abnormalities. An additional criterion in the differential diagnosis is the fact that these latter tremors are not relieved by the medications usually helpful in the Parkinson's disease, but they are sometimes temporarily relieved by the use of alcohol. States of emotional depression, especially if there is a great deal of psychomotor retardation with decrease in speech and motor activity, may also be difficult to differentiate from Parkinson's disease; and, of course, sometimes the two go together. Degenerative arthritis may impose some difficulties in diagnosis, especially in those cases of Parkinsonism in which there are contractures, deformities of the fingers and marked limitation of motion in the shoulders, elbows and neck. In the younger age group, multiple sclerosis, Wilson's disease, some muscle diseases, certain cerebellar ataxias and myxedema must be borne in mind. The tremors of hyperthyroidism, dementia paralytica, acute alcoholism and other poisonings are distinguished from those of Parkinson's disease by their rapid rate and lesser amplitude; occasionally both hyperthyroidism and Parkinsonism are present. Usually a careful clinical evaluation, bearing in mind the major manifestations of Parkinson's disease and looking for the earliest signs and symptoms, is sufficient for diagnosis without confusing the disease with other conditions. Diagnosis is most difficult in the very early cases in which tremor is not constant or in which slowing and loss of dexterity are the only symptoms. The differentiation between Parkinson's disease and symptomatic Parkinsonism has been mentioned above.

TREATMENT

The treatment of Parkinsonism may be divided into the use of drugs, the use of physical measures, a psychotherapeutic approach and the use of surgery. The major aspect of therapy in the past, and even today, is the use of drugs, although psychotherapy and physical therapy may give some assistance. Surgery, although it

has been tried for many years, must still be considered somewhat experimental.

Drug Therapy

The pharmacologic treatment of Parkinsonism, unfortunately, is largely palliative. Our major attempts to help the patient are directed at relief of the tremor and rigidity. Many drugs have been used, and it is quite characteristic of the disease that certain pharmaceutical preparations, or combinations of them, may be helpful in one case, whereas other drugs or combinations may be of more value in another. Patients with postencephalitic Parkinsonism not only show greater response to drug therapy but can tolerate much larger doses, without side effects, than patients suffering from the idiopathic or arteriosclerotic varieties.

The principal drugs used in the past were the solanaceous alkaloids—atropine, scopolamine, stramonium and hyoscyamus. These, probably by sedative action on lower brain centers, control the rigidity to a certain extent and the tremor to a lesser degree. The usual dose of either atropine or scopolamine is 0.4–0.6 mg. orally three times a day; the amount may be gradually increased to tolerance but must be decreased if side effects or toxic symptoms appear. Bulgarian belladonna and synthetic preparations of the solanaceous alkaloids, such as Bellabulgara, Vinobel and Rabellon, have also been used with some benefit. Owing to their atropine-like action, all of these drugs may cause dry mouth, pupillary dilatation with blurred vision, flushing and, in older persons, delirium, confusion and urinary retention. They continue to be valuable drugs for many patients, but have largely been replaced in therapy by certain synthetic preparations having antispasmodic, anticholinergic and antihistaminic effects. Consequently, the above-named substances are mainly used for patients who do not show response to some of the newer drugs.

The drugs which are most widely used today for the treatment of Parkinsonism are trihexyphenidyl (Artane) and cycrimine (Pagitane). Therapy is usually started with doses of 1–2 mg. of the former three times daily, or 1.25 mg. of the latter, in idiopathic and arteriosclerotic cases; in postencephalitic patients, larger doses (2–5 mg. of the former or 2.5 mg. of the latter)

may be used at the onset. The amount can be gradually increased to tolerance. The side reactions and toxic effects are similar to those of scopolamine and atropine, although either nausea or vertigo is not uncommon. Other synthetic preparations may also be of value in selected patients and in those who show little response to the above medications. Benztropine methanesulfonate (Cogentin) may be helpful if rigidity is an outstanding symptom. It has a rather prolonged action and is best given only at bedtime, or sometimes twice daily. The usual dose is 0.5 mg. in older patients and 2 mg. in postencephalitic cases. Ethopropazine hydrochloride (Parsidol) may aid in the relief of both rigidity and tremor. Therapy should begin with a small dose of this drug (10 mg. three times daily), with a gradual increase to 50 mg. three times daily at the end of 1 month. Procyclidine hydrochloride (Kemadrin) may also be helpful for both rigidity and tremor. Treatment should start with 2.5 mg. three times daily, with a gradual increase in the dose. Inasmuch as the patient with Parkinsonism may show a varying response to drugs, it is often worthwhile to try more than one of the foregoing, either alone or in combination. Because of the variability of tolerance and susceptibility to toxic symptoms, dosage must be individualized. With all of these drugs, it is important to bear in mind that therapy should be started with small doses and the amount administered increased gradually; by doing this, it may be possible to avoid side effects and toxic reactions.

Certain of the antihistaminic drugs, while of doubtful value when used alone, seem to have a synergistic action when given with the above preparations. The two that are used most often are phenindamine (Thephorin) in doses of 25 mg. or diphenhydramine hydrochloride (Benadryl) in doses of 25 or 50 mg. three times daily. Because the latter quite often causes drowsiness in patients with Parkinsonism, it is often best to try the former first. If lethargy, depression and fatigue are prominent symptoms, amphetamine or dextro-amphetamine in doses of 5 mg. morning and noon, or a 10-mg. delayed release capsule in the morning, should be added. These may also neutralize the sedative action of the other drugs and stimulate the patient so that motor activity is easier. If the patient is tense or agitated, sedatives or tranquilizers may be necessary. Chlorpromazine, meprobamate, reser-

pine or barbiturates in small doses may be tried for daytime relaxation or for their hypnotic action at night. Patients with Parkinsonism, however, and especially elderly ones, often react poorly to barbiturates; and if a sedative or hypnotic is necessary, it is best to use one that does not contain barbiturates. It must be borne in mind, also, that chlorpromazine and reserpine may cause Parkinson-like symptoms in some patients, and so their routine use in patients who already have the disease should be avoided; if used, the dose should be small and the patient should be examined frequently.

Physical Measures and Physical Therapy

Patients with Parkinsonism should be encouraged to be as active as possible, and every attempt should be made to have them continue with their usual occupations as long as possible, even if only on a part-time basis. If it is not possible for them to do so, especially if bradykinesia and rigidity are prominent symptoms, physiotherapy becomes an essential part of therapy. It should then be carried out regularly throughout the years to prevent and correct contractures and postural deformities. It should consist of active muscle stretching, resistance exercises, gait and movement training, and correction of faulty posture and balance. If the patient is confined to bed, the physiotherapy may have to be limited to passive range of movement exercises, muscle stretching and massage. In general, however, simple heat and massage are not of much help.

It is often worthwhile to simplify the life of the patient—the routine activities of daily living, such as dressing, shaving and eating. Clothing and shoes should be used that are easy to put on and remove (elimination of buttons and the use of clip ties and shoes without laces). An electric razor should replace the safety razor, if possible. It will be easier for the patient to rise from a chair if he is given one with the front legs a little shorter than the back ones. It must be borne in mind that slowing of activity is one of the symptoms of the disease, and the patient should be allowed extra time for routine tasks and must not be hurried. It is extremely important to encourage the patient to undertake as much activity as possible. If he is no longer able to be gainfully

employed, he should be given routine tasks and minor chores to do and be stimulated to take frequent walks or to swim in warm water. Travel and hobbies that interest and amuse the patient are helpful.

Every effort should be made to retard progression of the stooped posture and the contractures and deformities that are often a part of the disease. There is no specific apparatus that is of value, but it is often helpful to encourage the patient to use a cane if his gait has become quite difficult. This may not only help him to maintain a more erect posture and to have increased confidence in his ability to walk alone, but it may also decrease the tendency toward stumbling and falling. A fracture of a hip or arm may further incapacitate the patient, and his disability may be markedly increased after a period of forced recumbency. Rails next to his bed to help him turn over without assistance, and rails next to the bathtub and toilet, may make the patient more self-sufficient. Recently a laryngeal contact microphone has been described which may help those patients with marked weakness of voice converse with their attendants and friends (9).

Emotional Treatment and Psychotherapy

Unusual emotional responses to Parkinsonism must be watched for at all times. Many patients fail to adjust well to their illness and are disturbed by the presence of rigidity and tremor. They tend to withdraw into the seclusion of their homes with the onset of conspicuous signs of the disease. The physician should encourage and support any efforts to maintain work and social situations within the bounds of feasibility. Depressive reactions may be noted by failure to take medication regularly, complaints that the drugs cause unusual reactions, and greater incapacity than is in accord with the objective findings. Attempts should be made to counteract such depression by reassurance and suggestion, by encouraging more activity and social contacts and by interesting the patient in new hobbies.

It is only in rare cases, in which there is very profound depression, that the help of a psychiatrist is needed. Every physician can and often does employ psychotherapy, often without realizing it. This may be accomplished in many ways for the patient with

Parkinsonism (12). In the first place, the patient must be oriented regarding the nature of his illness; many persons have mistaken concepts regarding the progression and prognosis of this disease and may anticipate total incapacity or paralysis within a short period of time or, worse still, mental enfeeblement. Next the physician should have real concern for the patient's symptoms and ailments and should lend a sympathetic ear to his personal problems. Finally, he should give confident and constant assurance not only to the patient but also to the members of his family. Many of the newer antidepressant drugs may help to counteract the despondency that sometimes develops, but they must be used with discretion, since some of them have been shown to produce Parkinson-like symptoms. The rare patient who develops organic intellectual deterioration with or as part of his disease may need institutional care.

Surgical Treatment

Investigative and surgical approaches of various types have been made in the attempt to relieve the symptoms of extrapyramidal disease and, incidentally, to arrive at a better understanding of the basic pathophysiology of the clinical conditions described above (10). It has long been known that either injection of procaine into the involved muscles or section of either the anterior or posterior nerve roots will decrease rigidity, although these measures will not influence tremor. Both of these procedures interrupt either the afferent or efferent pathway of the proprioceptive reflex arc; neither is a suitable or practical procedure in treatment. Furthermore, it is also well known that the tremor of Parkinsonism is lessened or abolished by a capsular hemiplegia, at least for the duration of the paralysis; but the impairment of motor function may be more incapacitating than the hyperkinesia. Based on the above clinical observations, and more recently on the neurophysiologic demonstrations of the connections and functions of the extrapyramidal complex and its individual components, surgical measures have been utilized in an attempt to mitigate the symptoms of disease. Such procedures have, in isolated cases, brought about marked clinical improvement; but no single operative approach advanced to date has become a standard therapeutic tool. This is easily understood

when one realizes that there is, as yet, no unanimity of opinion regarding the exact pathophysiology of the symptoms of extrapyramidal disorders.

The surgical approaches thus far have been various; and attention has been directed to the cerebral cortex, internal capsule, basal ganglia, pallidofugal fibers and spinal cord. Horsley, in 1908, first excised the motor cortex for the relief of athetosis. Later resections were made of areas 6, 4, or both, of the frontal cortex, or interruption of the U fibers between areas 4 and 6, for the relief of Parkinsonism and other extrapyramidal syndromes (Bucy, Meyers, Klemme and others); hyperkinetic phenomena were alleviated more than rigidity. Browder made selective section of fibers in the anterior limb of the internal capsule, together with ablation of the adjacent portion of the putamen, for the relief of both tremor and rigidity in Parkinson's disease. Meyers has removed parts of the caudate and lenticular nuclei, along with interruption of fibers in the internal capsule; but later he sectioned the pallidofugal fibers (fasciculus and ansa lenticularis) in Parkinsonism. Electrolytic destruction (ansotomy) and coagulation of the ansa lenticularis have been carried out for Parkinson's disease by Fenelon, Guiot, and Spiegel and Wycis. Walker and Meyers have sectioned the cerebral peduncle for Parkinsonism and other diseases characterized by hyperkinesia; Putnam, Ebin and Oliver have sectioned the pyramidal and parapyramidal tracts in the spinal cord. Cooper (6) has utilized surgical occlusion of the anterior choroidal artery in treating Parkinsonism; and Narabayashi (23), Cooper (6), Spiegel and Wycis (27) and others have produced lesions in the globus pallidus, its connections or associated structures, by the injection of procaine in oil or alcohol or by electrolytic means.

Recent interest has been concentrated on the last-mentioned approaches, which have brought relief to many well-selected patients. The most significant amelioration of symptoms has been reported following the production of minute lesions in the basal ganglia and related structures by the introduction of alcohol (chemopallidectomy or chemothalamatomy) (6) or by electrocoagulation, surgery or the use of ultrasound (21). Such lesions in the medial portion of the globus pallidus have been most effective for relief of rigidity, in the ventrolateral portion of the

thalamus for relief of tremor and in the ansa lenticularis or related tracts or the substantia nigra for either. Many patients have received definite benefit, possibly permanent, from these procedures; but serious complications have also been reported in some cases. Such surgery is most beneficial if the symptoms of disease are predominantly unilateral, but it does not give much relief for symptoms such as facial masking, loss of associated movements or akinesia. It should *not* be carried out in the elderly, in those with evidence of cardiac, vascular or renal disease or in patients showing evidence of pyramidal tract involvement or intellectual deterioration. Surgery should never be considered *until* the patient has had an adequate trial of drug therapy and is willing to assume the risks, expense and inconvenience of such an approach.

It should be an encouragement to both patient and physician that research into the etiology, pathophysiology and treatment of Parkinsonism is continuing. While surgery thus far has not completely explained the normal and pathologic physiology of the so-called "extrapyramidal complex," it has contributed to our understanding of the functions and dysfunctions of this level of motor integration and has served to broaden our concepts of the anatomic and physiologic bases of the extrapyramidal disorders. Continuation of the carefully controlled work that has been carried out thus far may eventually lead to a safer and more consistently effective surgical approach. On the other hand, pharmaceutical chemists and pharmacologists are investigating other drugs in the hope of finding a more suitable one (one without side effects). Most of the agents tried are synthetic preparations, similar chemically to the ones in use; but it may be that widely differing substances may be of value, as indicated in the recent, but still unproved, report of the effect of tolbutamide (Orinase) in the treatment of Parkinsonism (14).

Although there is no definite cure for Parkinsonism, the present prognosis for patients is by no means hopeless. The use of currently available drugs, either alone or in combination, is helpful in a large percentage of cases, especially if combined with physical measures and with a proper psychologic understanding of the patient and his disorder. It is hoped that future developments in surgery may eventually give even more relief.

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